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Adult vaccination against tetanus and diphtheria: the European perspective

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Summary

Besides immunizations against influenza, *Streptococcus pneumoniae* and herpes zoster, which are recommended specifically for elderly people, regular booster vaccinations against tetanus, diphtheria and in some cases pertussis and polio are recommended in many European countries for adults, including elderly people. Vaccination recommendations for adults differ greatly between individual countries and coverage data is scarce. Tetanus-specific antibody concentrations are generally higher than diphtheria-specific antibodies, and a substantial proportion of adults, and particularly of elderly people, do not have protective antibody concentrations against diphtheria. Antibody levels increase upon booster vaccination in all age groups, but diphtheria-specific antibody concentrations remain below protective levels in some older individuals, even immediately after vaccination and long-term protection is frequently not achieved. Future vaccination strategies should therefore include regular and well-documented booster shots, e.g. against tetanus and diphtheria, throughout life.

Keywords: adult vaccination, coverage, diphtheria, elderly people, tetanus

Introduction

The exceptional success of childhood vaccination is undisputed, but the importance of vaccination throughout adulthood, and particularly of the older population, is frequently underestimated. In many countries, vaccinations against influenza, *Streptococcus pneumoniae* and herpes zoster are recommended specifically for elderly people. Influenza is the only vaccine for which vaccination coverage of adults is reasonably well documented in Europe, and tremendous differences are observed between European countries. Mereckiene *et al.* report seasonal influenza coverages of the older population for the years 2008–10. Whereas more than 70% of elderly people received the influenza vaccine in the Netherlands and the United Kingdom, in some countries, such as Latvia and Estonia, coverage was below 10%. The majority of the European countries achieve vaccination rates of approximately 50–60% in this age group [1].

In addition, regular booster shots against tetanus and diphtheria – in some cases in combination with pertussis – are recommended throughout adulthood in many countries. This review will focus upon tetanus and diphtheria, as recommendations for vaccination against pertussis are extremely inconsistent between European countries. Vaccines against tetanus and diphtheria are among the most frequently used vaccines worldwide. These vaccines were introduced in Europe in the 1920s to 1930s and in many countries general vaccination has been performed since the 1940s. Toxins produced by *Clostridium tetani* or *Corynebacterium diphtheriae*, respectively, cause the pathological symptoms of tetanus and diphtheria. The toxins can be detoxified by formalin inactivation, and adsorbed to

aluminium hydroxide or phosphate these toxoids comprise the vaccines against tetanus and diphtheria. Vaccination against tetanus and diphtheria is performed usually using combined vaccines. For infant vaccination, pentavalent or heptavalent vaccines containing tetanus, diphtheria, pertussis, poliomyelitis and *Haemophilus influenzae* type B antigens with or without hepatitis B antigen are used widely. Various vaccine formulations are licensed, but most contain 25–30 Lf (limit of flocculation) diphtheria toxoid and 40 Lf tetanus toxoid per dose. For adolescents and adults a combination of tetanus (20 Lf) and diphtheria toxoid (2 Lf per dose) is used (Td), which can also be combined with acellular pertussis (aP) and/or inactivated polio (IPV) antigens.

This review summarizes data on vaccination recommendations and coverage in Europe as well as on serum antibodies and immunogenicity in adults, particularly in elderly people.

Vaccination recommendations and coverage in Europe

Incidences of tetanus and diphtheria are low in Europe, with 161 cases of tetanus and 36 cases of diphtheria per year (mean from 2009 to 2014) [2], but vaccination against these diseases is still of importance. In Italy 80·2% of the tetanus cases between 2001 and 2010 occurred in people aged more than 65 years. The incidence in females was more than threefold higher than in males during this time-period [3]. Increased incidence in elderly people, and particularly in older women, has also been reported in Australia [4]. *C. tetani* is found ubiquitously in soil and infection occurs mainly through contaminated wounds. Due to this mode of transmission, vaccination does not decrease the prevalence of the bacteria and there is no herd immunity effect, which means that every individual needs to be vaccinated in order to be protected. In contrast, *C. diphtheriae* is transmitted from person to person via droplets. In the early 1990s a large outbreak with more than 140 000 cases and more than 4000 deaths occurred in the states of the former Soviet Union, demonstrating that the pathogen is still present and can spread efficiently in a partially unprotected population [5].

The World Health Organization (WHO) currently recommends a primary vaccination series against tetanus and diphtheria during childhood and regular booster vaccinations throughout life, and this recommendation is implemented in many countries [3,4]. All European countries recommend three or four doses of tetanus and diphtheria vaccine in the first 2 years of life and one to three childhood/adolescence booster shots (age 2–17 years). The majority of the European countries recommend regular booster vaccinations throughout adulthood every 10–20 years. Recommendations in Croatia and Poland include only a single booster shot during adulthood. Several countries do not recommend vaccination during adulthood. Only a few countries have issued specific recommendations for elderly people, with shortened booster intervals in Austria, France and Liechtenstein and additional doses in Croatia and Spain. All other countries also implement adult recommendations for elderly people. Tetanus and diphtheria vaccination is generally recommended as a combined vaccination; however, Croatia, the Czech Republic, Malta, Romania and Slovenia issued discordant recommendations for tetanus and diphtheria. A comprehensive overview of all European recommendations for vaccination against tetanus and diphtheria is shown in Table 1.

Data on vaccination coverage of adults are scarce. A large survey by the Vaccine European New Integrated Collaboration Effort (VENICE) consortium in 2010/2011 in all 29 European Union/European Economic Area (EU/EEA) countries showed that data on coverage for adult influenza vaccination were available for 20 of 29 countries. In this study, coverage estimates for adult tetanus vaccination have been reported for only six countries and were between 61 and 74%. Similar data for diphtheria vaccination were available for five countries and ranged from 61 to 74% in countries with recommendations for regular booster shots. In contrast, the coverage estimate was only 34% in France, where adult booster vaccinations against diphtheria were not indicated in the official schedule at the time of the survey [7]. Bodeker *et al.* reported that 75·6% of adults, including elderly people, had been vaccinated against tetanus within the last 10 years based on a telephone survey in Germany [8].

Tetanus- and diphtheria-specific antibody concentrations in adults and elderly people

The well-accepted correlates of protection for tetanus and diphtheria are toxoid-specific antibodies which neutralize the bacterial toxins upon infection. Most studies use enzyme-linked immunosorbent assay (ELISA)-based methods to quantify serum antibodies. A level of 0·01 IU/ml is considered frequently to provide partial protection but, generally, concentrations above 0·1 IU/ml are defined as protective [9,10].

In a cross-sectional study in Austria, tetanus-specific antibody concentrations were shown to decline with increasing time since the last vaccination. At all timepoints antibody concentrations were lower in elderly people compared to young adults [11]. These results are in concordance with data from Israel [12]. In a longitudinal observation, the half-life of tetanus antibodies has been estimated to be 11 years [13], and similar results have also been reported for diphtheria-specific antibodies [14,15]. Tetanus- and diphtheria-specific antibody concentrations are frequently below the levels considered to be protective ($> 0{\cdot}1$ IU/ml) for adults and particularly for elderly people, as shown in cohorts from Spain [16], Belgium and Australia [17], Italy [3] and France [18] (Table 2). On average,

Table 1. Official vaccination recommendations against tetanus and diphtheria for European countries [6]

	Infants	Children	Adolescents	Adults	Elderly*
Tetanus	2–23 months	2–8 years	9–17 years	18–60 years	> 60 years
Austria	2 + 1	1	1	Every 10 years	Every 5 years
Belgium	3 + 1	1	1	Every 10 years	
Bulgaria	3 + 1	1	2	Every 10 years	
Croatia	3 + 1	2	1	1	1
Cyprus	3 + 1	1	1	Every 10 years	
Czech Republic	3 + 1	1	1	Every 10–15 years	
Denmark	2 + 1	1	–	–	
Estonia	3	2	1	Every 10 years	
Finland	2 + 1	1	1	Every 10 years	
France	2 + 1	1	1	Every 20 years	Every 10 years
Germany	3 + 1	1	1	Every 10 years	
Greece	3 + 1	1	1	Every 10 years	
Hungary	3 + 1	1	1	–	
Iceland	2 + 1	1	1	–	
Ireland	3	1	1	–	
Italy	2 + 1	1	1	Every 10 years	
Latvia	3 + 1	1	1	Every 10 years	
Liechtenstein	3 + 1	1	1	Every 20 years	Every 10 years
Lithuania	3 + 1	1	1	Every 5–10 years	
Luxembourg	3 + 1	1	1	Every 10 years	
Malta	3 + 1	1	1	–	
The Netherlands	3 + 1	1	1	–	
Norway	2 + 1	1	1	–	
Poland	3 + 1	1	1	1	
Portugal	3 + 1	1	1	Every 10 years	
Romania	2 + 1	2	1	Every 10 years	
Slovakia	2 + 1	1	1	Every 15 years	
Slovenia	3 + 1	1	1	Every 10 years	
Spain	3 + 1	1	1	–	1
Sweden	2 + 1	1	1	Every 20 years	
United Kingdom	3	1	1	–	

	Infants†	Children‡	Adolescents‡	Adults§	Elderly*§
Diphtheria	2–23 months	2–8 years	9–17 years	18–60 years	>60 years
Austria	2 + 1	1	1	Every 10 years	Every 5 years
Belgium	3 + 1	1	1	Every 10 years	
Bulgaria	3 + 1	1	2	Every 10 years	
Croatia	3 + 1	2	1	1	
Cyprus	3 + 1	1	1	Every 10 years	
Czech Republic	3 + 1	1	1	–	
Denmark	2 + 1	1	–	–	
Estonia	3	2	1	every 10 Every	
Finland	2 + 1	1	1	Every 10 years	
France	2 + 1	1	1	Every 20 years	Every 10 years
Germany	3 + 1	1	1	Every 10 years	
Greece	3 + 1	1	1	Every 10 years	
Hungary	3 + 1	1	1	–	
Iceland	2 + 1	1	1	–	
Ireland	3	1	1	–	
Italy	2 + 1	1	1	Every 10 years	
Latvia	3 + 1	1	1	Every 10 years	
Liechtenstein	3 + 1	1	1	Every 20 years	Every 10 years
Lithuania	3 + 1	1	1	Every 5–10 years	

Table 1. *Continued*

	Infants†	Children‡	Adolescents‡	Adults§	Elderly*§
Diphtheria	2–23 months	2–8 years	9–17 years	18–60 years	>60 years
Luxembourg	3 + 1	1	1	Every 10 years	
Malta	3 + 1	0	1	–	
The Netherlands	3 + 1	1	1	–	
Norway	2 + 1	1	1	–	
Poland	3 + 1	1	1	1	
Portugal	3 + 1	1	1	Every 10 years	
Romania	2 + 1	1	1	Every 10 years	
Slovakia	2 + 1	1	1	Every 15 years	
Slovenia	3 + 1	1	0	–	
Spain	3 + 1	1	1	–	1
Sweden	2 + 1	1	1	Every 20 years	
United Kingdom	3	1	1	–	

2 + 1: two doses (1- or 2-month intervals), 3rd dose 6–12 months later. 3 + 1: three doses (1- or 2-month intervals), 4th dose 6–12 months later. 3: 3 doses (1- or 2-month intervals). *Same as for adults, if not noted otherwise. †Vaccine containing high dose of diphtheria toxin (D). ‡Depending on the country, children older than 4–12 years receive vaccine containing reduced dose of diphtheria toxin (d). §Vaccine containing reduced dose of diphtheria toxin (d). Differences between tetanus and diphtheria recommendations are shown in grey.

the last vaccination dated back longer in people without protective antibodies, as shown for diphtheria (16·1 years *versus* 7·2 years) [18]. In a cohort of adults above the age of 40 years, for whom the last vaccination dated back more than 20 years, 18·2 and 55·5% were not protected against tetanus and diphtheria, respectively [19]. A large study conducted in seven European countries (Italy, Germany, Finland, France, the Netherlands, England/Wales and Sweden) between 1995 and 1998 also showed substantial differences between countries, and a larger proportion of older adults was below protective antibody concentrations for diphtheria compared to younger adults. As an example, between 5 and 40% of young adults (aged 25–29 years), but approximately 30–70% of older adults (aged 60–64 years), had antibody concentrations below the protective level [21]. At this time-point only Germany recommended regular booster immunizations for adults. An Austrian study of people aged more than 60 years undertaken by our group in 2005 revealed that 12 and 65% of the participants were not protected against tetanus or diphtheria, respectively [20] (Table 2). Interestingly, 53% of a young cohort (aged 20–40 years) recruited 5 years later were also not protected against diphtheria, whereas all participants were protected against tetanus (Weinberger, unpublished data). Several studies reported higher antibody levels in males compared to females. The most probable explanation for this phenomenon is that males are usually vaccinated during or prior to military service and/or receive booster vaccination after injury more frequently [21–24].

Immune responses to booster vaccination against tetanus and diphtheria

Several studies have analysed the antibody responses after a single booster shot of tetanus and diphtheria vaccine in different age cohorts using different vaccine formulations (Td, TdaP, Tdap-IPV, Td-IPV). No major differences were observed when comparing the different combination vaccines. Tetanus-specific antibody concentrations were always higher than diphtheria-specific ones, leading to a larger percentage of people protected against tetanus compared to diphtheria. The results summarized in this section represent antibody measurements approximately 4 weeks after vaccination unless stated otherwise. A study performed in Denmark showed 100% [95% confidence interval (CI) = 99·1–100] and 98·5% (95% CI = 96.8–99·4) seroprotection against tetanus and diphtheria with geometric mean concentrations (GMCs) of antibodies being 35.03 IU/ml (95% CI = 31.60–38.83) and 4.6 (IU/ml) (95% CI = 4.03–5.26) in people aged 18–55 years. Many studies do not consider elderly people as a specific age group, but give comparisons between adults below or above the age of 40 years. Grimprel *et al.* demonstrated higher seroprotection (tetanus 100 *versus* 99·2%; diphtheria 94·1 *versus* 81·0%) and GMCs (tetanus 7·542 IU/ml, 95% CI = 6·661–8·536 *versus* 5·247 IU/ml, 95% CI = 4·365–6·308; diphtheria 2·010 IU/ml, 95% CI = 1·615–2·502 *versus* 0·371 IU/ml, 95% CI =0·279–0·493) in the younger age group after vaccinations with dTap-IPV. Similar results were obtained with other vaccine formulations in this study [25] and by others [17,26,27]. Data from several studies conducted in Australia, Belgium, France, Germany, the Netherlands and Spain were compiled comparing vaccine-induced antibody responses in two older age groups, namely 55–64 and 65–93 years. Interestingly, seroprotection was lower in the oldest age group for tetanus (88·9%, 95% CI = 82·1–93·8 *versus* 98·8%, 95% CI = 95·7–99·9) but

Table 2. Percentage of people without protective antibody concentrations (> 0·1 IU/ml) against tetanus and diphtheria

Tetanus					
Age group (years)	% Unprotected	95% CI	Country	Date of study	Reference
15–24	13	10·5–15·9	Italy	2003/2004	3
45–64	56·6	51·7–61·4	Italy	2003/2004	3
65–75	73·4	67·8–78·6	Italy	2003/2004	3
75–84	72·1	66·1–77·7	Italy	2003/2004	3
≥85	82·9	66·4–93·4	Italy	2003/2004	3
18–30	9·5	n.a.	Spain	1995–1998	16
45–79	69·4	n.a.	Spain	1995–1998	16
18–40	5·7	3·9–8·1	Belgium/Australia	n.a.	17
41–73	24·8	20·2–28·9	Belgium/Australia	n.a.	17
18–60	1·5*	n.a.	France	2005	18
>40	18·8†	14·7–23·4	Germany/France	n.a.	19
61–87	12	5–19	Austria	2005	20
Diphtheria					
Age group (years)	% Unprotected	95% CI	Country	Date of study	Reference
18–30	61·7	n.a.	Spain	1995–1998	16
45–79	80·96	n.a.	Spain	1995–1998	16
18–40	21·4	17·9–25·2	Belgium/Australia	n.a.	17
41–73	29·2	24·4–34·5	Belgium/Australia	n.a.	17
18–29	3*	0·1–5·9	France	2005	18
50–60	37·3*	25·4–49·2	France	2005	18
>40	55·5†	49·9–60·9	Germany/France	n.a.	19
61–87	65	55–75	Austria	2005	20

*This study included only people who had received all tetanus and diphtheria booster vaccinations according to official recommendations throughout life. †This study included only people for whom the last vaccination dated back more than 20 years. CI = confidence interval; n.a. = not available.

not for diphtheria (83·3%, 95% CI = 75·7–89·4 *versus* 82·4%, 95% CI= 75·7–87·9), and these findings were confirmed when analysing GMCs. It was also demonstrated that the magnitude of the antibody response is reduced with increasing time since the last vaccination [28]. It has been suggested to administer a complete primary series (three doses) of Td vaccine to adults if the last vaccination dates back more than 20 years. Dominicus *et al.* followed this approach in a cohort of adults older than 40 years (mean age 60·2), and showed that the first dose is sufficient to provide protection against tetanus (seroprotection rate 98·5%, 95% CI = 96·5–99·5) and that antibody concentrations are equal after the first and third doses. In contrast, whereas only 82·4% (95% CI = 77·9–86·4) of the cohort were protected against diphtheria after the first dose, protective antibody concentrations were achieved for 94·6% (95% CI = 91·5–96·8) after completion of the primary series. This increased protection was also reflected by GMCs (first dose: 0·813, 95% CI = 0·624-1·059; third dose 1·489, 95% CI = 1·262–1·757) [19]. Direct comparisons of young (< 40 years) and older (> 60 years) adults are rare. Weston *et al.* published data on cohorts of adults (19–64 years, mean age 46) [29] and elderly people (> 65 years) [30] showing almost complete protection against tetanus for both age groups, with higher GMCs in the younger group (6·5 IU/ml, 95% CI = 6·0–7·0 *versus* 3·4 IU/ml, 95% CI = 2·7–4·3). Differences were observed for diphtheria, with only 4·9% (95% CI = 3·4–6·8) of the younger, but 13·3% (95% CI = 6·7–20·1) of the older cohort being below protective antibody concentrations. These results correspond well with data from our own studies, where we reported lower GMCs against diphtheria (1·09 IU/ml, 95% CI = 0·81–1·46 *versus* 4·16 IU/ml, 95% CI = 2·36–7·34) in old (> 60 years) compared to young (20–33 years) adults, but no age-related differences in tetanus-specific antibodies [31]. Ten per cent of the older participants did not develop protective diphtheria-specific antibody concentrations even 4 weeks after vaccination. A long-term follow-up was performed in a proportion of the old cohort and 5 years later antibody concentrations had dropped substantially, reaching approximately the level before the first booster vaccination. We administered a second booster vaccination at this time-point, and similar to the first booster all participants developed protective antibody concentrations against tetanus, but again 6% did not respond to the diphtheria vaccine

[20]. Another 5 years later, antibody concentrations had again dropped to the levels observed at the first enrolment (Weinberger, unpublished data). In conclusion, single-booster shots late in life do not seem to elicit sufficient and long-lasting antibody responses in a substantial portion of elderly people. In summary, most studies showed lower antibody responses in older people. This might be due to age-related defects of the immune system [32] and/or differences in the vaccination history.

Importance of vaccination documentation and combination vaccines

Vaccination against tetanus is recommended when wounds which could potentially be contaminated with soil (e.g. after accidents, outdoor injuries, etc.) are treated and no recent vaccination is documented. Official recommendations specify the use of a combined tetanus/diphtheria vaccine in such cases in order to avoid multiple tetanus shots and a lack of diphtheria vaccination. Nevertheless, single tetanus vaccinations after injuries are still common in clinical practice. In our above-mentioned Austrian study, only 31% of the participants had received their last tetanus/diphtheria vaccination as a combined vaccine [20]. A recent survey based on health-care insurance data in Germany showed that, depending on the region, 10–40% of vaccinations against tetanus in Germany are performed as a single vaccination and do not use combination vaccines. The use of combined vaccines decreases with increasing age of the vaccinees [33].

Appropriate vaccination documentation is crucial for timely administration of booster vaccinations. It is particularly difficult to assess reliably correct primary vaccination in childhood and the number of booster shots administered throughout life, as vaccination documentation is poor for many older adults. Efforts to retrieve information about vaccination history for our above-mentioned Austrian study were only partially successful, as it was not possible to determine the time-point of the last vaccination in 10 and 53% of the cases for tetanus or diphtheria, respectively [20]. A survey in France in 2010/2011 revealed significant discrepancies between self-reported and confirmed vaccination status for tetanus and diphtheria; 20·5% (95% CI = 15·5–26·3) or 36·7% (95% CI = 29·5–44·4%) of people who thought that they were up to date with their vaccinations were actually not, according to their vaccination documents [34]. It has been shown that the number of vaccine doses received in life decreases with age in France. Young adults (< 30 years) received on average 7·1 (95% CI = 6·9–7·2) doses of tetanus vaccine, which corresponds well with recommendations of five doses during childhood/adolescence and 10 year-booster intervals afterwards. However, people aged 50–60 years received only 5·7 (95% CI = 4·6–6·8) doses during their lifetime, indicating a lack of regular booster vaccinations [18].

Outlook

Future vaccination strategies should include regular and well-documented booster shots, e.g. against tetanus and diphtheria throughout life, as post-booster antibody concentrations correlate with pre-booster antibody concentrations [31]. The success of primary vaccination late in life for people without adequate priming during childhood remains to be elucidated, as the problem of memory generation late in life is well documented in animal models [35,36]. Antibody concentrations against diphtheria are always substantially lower than against tetanus. As mentioned above, the vaccine used for booster shots contains only a reduced dose of diphtheria toxoid, which might limit its capacity to induce sufficient and long-lasting immunity. Considerations regarding improved vaccines against diphtheria (e.g. higher antigen dose, alternative adjuvant) should also be taken into account.

Currently, recommendations and their implementation differ greatly between European countries. Efforts are made to harmonize vaccination schedules across Europe for children, but should not stop there. It is important to advocate vaccination as a lifelong intervention from infants to elderly people [37–39]. Awareness for the importance of vaccination is high in the paediatric setting and has increased during recent years among geriatricians. Unfortunately, vaccination is still frequently neglected during the decades of adult life, and efforts should be made to check vaccination documentation regularly for all age groups in order to provide timely booster vaccinations and to close potential vaccination gaps.

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The author declares no disclosures.

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